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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,267	12/02/2003	Peng Cho Tang	034536-0906	4675

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 02/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/725,267	TANG ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 10-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 10-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/2/03; 10/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a Division of 09/819,698, filed 3-29-01 (now US 6,683,082).

A restriction requirement of five groups was presented in the parent application 09/819,698. The preliminary amendment of 12-2-03 has defined variables A, B, D and E according to group II of the restriction requirement in the parent application.

Claims 7-9 are cancelled.

Claims 1-6 and 10-37 are pending.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-6 and 10-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. Claims 1-6, 10 and 18 recite the term "*prodrug*" which has indefinite metes and bounds because it is unclear what moiety would constitute a "prodrug", and where its location would be (i.e., on ring Q? or on variables R^1, R^2, and R^3-R^6). Furthermore, R^3-R^5 represent many 'ester' groups like *sulfonyl, sulfonamide, carboxyl, O-carbamyl, N-carbamyl,* etc., which could also be a form of "prodrug". Therefore, "prodrug" would be the broader limitation of functional groups represented by R^3-R^5.

b. Claim 1 also recites variable Z representing a "*polar group*". Although the specification briefly defines what constitutes a "*polar group*", it is still unclear what other moieties would be qualified as a "*polar group*". Note, said definition includes not only functional groups, but also rings. Thus, it is unclear as to what structural make-up of such a group is.

c. Claim 10 recites "*A method for the modulation of the catalytic activity of a protein kinase...*", which has indefinite metes and bounds because it is unclear what indication is intended by such a mode of action. Claims 11-17 depend on claim 10, and thus, are also indefinite for the same reason. The claim language reads on diseases not yet known to be caused by or affected by such an action, or in way not yet understood. The test for determining compliance with 35 U.S.C. 112, 2nd paragragph is whether applicants have clearly defined "their" invention not what may be discovered by future research as this type of claim language clearly requires.

d. Claim 19 recites "*A method for treating or preventing a protein kinase related disorder...*", which has indefinite metes and bounds because it is unclear what indication is intended by such a mode of action. Claims 20, 21, 23, 25, 28, 30 (ultimately) depend on claim 19, and thus, are also indefinite for the same reason. Again, the claim language reads on diseases not yet known to be caused by or affected by such an action, or in way not yet understood.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Written Description for "prodrug":** Claims 1-6 and 10-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification fails to describe the limitation of "*prodrug*" recited in claims 1-6,10 and 18 in terms of possible functional groups, their locations, and reaction conditions for forming such a "*prodrug*". Thus, the limitation of "*prodrug*" lacks a written description. Claims 11-37 are rejected as being dependent on claim 1, 10 or 18.

3. **Written Description for a tricyclic system:** Claims 1-6 and 10-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 recites the limitation of "*R^3 and R^4, R^4 and R^5,... may combine to form a six-member aryl or heteroaryl ring.*" Such a ring would fuse with the existing bicyclic core, and thereby would constitute a *tricyclic* system. The specification fails to describe a tricyclic system in terms of a process for preparing such a system, and bioassay to confirm the intended

pharmacological activity. The listed species are mostly substituted *2-oxoindole.* Thus, the limitation of a *tricyclic system* formed by a fused ring of R^3 *and* R^4, R^4 *and* R^5 does not have a written description.

Claims 2-6, and 10-37 are rejected as being dependent on claim 1.

4. **Scope of Enablement:** Claims 10-17 and 19-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of *small-cell lung cancer, breast cancer, ovarian cancer or prostate cancer*, does not reasonably provide enablement for the treatment of other diseases related to protein tyrosine kinase, serine-threonine kinase such as: *squamous cell carcinoma, astrocytoma, glioblastoma, bladder cancer, head and neck cancer, glioma, autoimmune disorder, restinosis, fibrosis, psoriasis, osteoarthritis, rheumatoid arthritis, hyper-proliferation disorder, inflammatory disorder, and angiogenesis, etc.*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

Claims 10-17 are drawn to "*a method for the modulation of the catalytic activity of a protein kinase...*" As pointed out in the 112/2nd rejection, such a method reads on the treatment of both known and unknown diseases. The claimed method also covers the treatment for an array of diseases as cited below:

> **[0135]** Thus, PK signal transduction results in, among other responses, cell proliferation, differentiation, growth and metabolism. Abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy (or other disorders related to uncontrolled angiogenesis and/or vasculogenesis).

[0148] Cell proliferative disorders, which may be prevented, treated or further studied by the present invention include cancers, blood vessel proliferative disorders and mesangial cell proliferative disorders.

[0149] Blood vessel proliferative disorders refer to angiogenic and vasculogenic disorders generally resulting in abnormal proliferation of blood vessels. The formation and spreading of blood vessels, or vasculogenesis and angiogenesis, respectively, play important roles in a variety of physiological processes such as embryonic development, corpus luteum formation, wound healing and organ regeneration. They also play a pivotal role in cancer development. Other examples of blood vessel proliferation disorders include arthritis, where new capillary blood vessels invade the joint and destroy cartilage, and ocular diseases, like diabetic retinopathy, where new capillaries in the retina invade the vitreous, bleed and cause blindness. Conversely, disorders related to the shrinkage, contraction or closing of blood vessels, such as restenosis, are also implicated.

[0150] Fibrotic disorders refer to the abnormal formation of extracellular matrices. Examples of fibrotic disorders include hepatic cirrhosis and mesangial cell proliferative disorders. Hepatic cirrhosis is characterized by the increase in extracellular matrix constituents resulting in the formation of a hepatic scar. Hepatic cirrhosis can cause diseases such as cirrhosis of the liver. An increased extracellular matrix resulting in a hepatic scar can also be caused by viral infection such as hepatitis. Lipocytes appear to play a major role in hepatic cirrhosis. Other fibrotic disorders implicated include atherosclerosis.

[0151] Mesangial cell proliferative disorders refer to disorders brought about by abnormal proliferation of mesangial cells. Mesangial proliferative disorders include various human renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection, and glomerulopathies. The PDGF-R has been implicated in the maintenance of mesangial cell proliferation. Floege et al., 1993, *Kidney International* 43:475-54S.

Note, the term "*hyper-proliferation*" alone covers an extensive list of biological growth processes including embryogenesis. Thus, the scopes of claims 10-17 are unduly broad.

Claims 19-21, 23, 25, 28, 30 are directed to "*a method for treating or preventing a protein kinase related disorder...*" Again, it is unclear what the intended disease is. The claimed method also covers the treatment of various diseases as cited above. Thus, their scopes are also unduly broad.

Claims 22, 24, 26, 27, 29, 31-35 are dependent claims that recite specific diseases. However, some of them are either not known to be related to protein tyrosine kinase (e.g., diabetes), or cannot be substantiated by the evidence provided in the specification.

Claims 36 and 37 depend on claim 19, and recite the organism to be "mammal" or "human". However, regarding the scope of treatment, they still carry the unduly broad scope of claim 19.

The amount of direction or guidance presented:

The specification provides various *in-vitro* assays. The *in-vitro* IC_{50} values are provided for *2-indolinone* compounds only. As for *in-vivo* assays, the specification briefly describes the procedure, but does not provide data for the actual tested compounds. Thus, based on the *in-vitro* data, one cannot conclude whether the claimed compounds actually have any activity on protein kinase since the tested compounds do not have structural similarity with the claimed compounds. Thus, the specification fails to provide adequate enablement for using the claimed compounds in the method recited in claims 10-17 and 19-37.

The state of the prior art:

As evident by the teachings of **Kimura et. al.** (US 6,063,782) and **Grundler** (US 5,534,515), compounds of substituted *pyrrolopyridazine* have the activity of inhibiting gastric acid secretion. Thus, the known pharmacological activity of *pyrrolopyridazine* is far from the activity to treat any of the disorders related to protein kinase or hyper-proliferation. Therefore, the state of the prior art does not support the method recited in claims 10-17 and 19-37.

The relative skill of those in the art:

Even with the advanced training, the skilled clinician would have to engage in extensive research to select an effective compound from the large Markush group of the claimed *pyrrolopyridazine* formula. Not only one has to determine an IC_{50} value, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for each compound. Given a large Markush group of the claimed formula, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary:

The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the specification only provides *in-vitro* data for *2-indolinone* compounds, which cannot be extrapolated to the claimed compounds due to structural difference.

Also, no compound has ever been found to treat diseases of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. Note, substantiation of utility and its scope is required when

utility is "speculative", or "sufficiently unusual". See ***Ex parte Jovanovics***, 211 USPQ 907, 909; ***In re Langer*** 183 USPQ 288. Also, see ***Hoffman v. Klaus*** 9 USPQ 2d 1657, and ***Ex parte Powers*** 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Thus, with such a limited teaching, the skilled clinician would have to engage in undue experimentation to use the claimed compounds in the methods recited in claims 10-17 and 19-37.

Double Patenting

The **nonstatutory double patenting** rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-3, 10-26, 28 and 29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 8, 9, 11 and 12 of U.S. Patent No. **6,465,507 B2**. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The instantly claimed *pyrrolopyridazine* formula overlaps with formula I of US'507, when formula I has the following substituents:

i. $(R^1)_m$ represents hydrogen, alkyl, aromatic or heteroaromatic ring – the scope of which corresponds to the scope of the instant variables R^3-R^6.

ii. The bicyclic system containing oxygen corresponds to the instant variable R^8 forms a heteroalicyclic ring fused to two adjacent atoms of the Q ring.

Formula I of US'507 differs from the claimed *pyrrolopyridazine* formula by having variables A, B, D and E representing more combinations of one or two nitrogen atoms. That is, the ring having A, B, D and E includes *pyridine, pyrimidine, pyrazine,* and *pyridazine.*

Such a difference constitutes a difference in scope. It would have been within the level of the skilled chemist to recognize that the claimed *pyrrolopyridazine* formula is a subgenus of formula I in US'507.

Thus, at the time that the invention was made, it would have been obvious to make and use the claimed *pyrrolopyridazine* formula in view of formula I in US'507.

Specification

6. The disclosure is objected to because of the following informalities:

Page 14, the structure for Q is missing variable Z.

Appropriate correction is required.

No pending claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Tamthom N. Truong
Examiner
Art Unit 1624

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2-2-06

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